

EXHIBIT F

WILMERHALE

May 2, 2006

Amy Kriger Wigmore

Via Federal Express

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Karen M. Robinson
Kirkland & Ellis LLP
655 Fifteenth Street, N.W.
Washington, DC 20005

Re: *Smith Kline & French Laboratories, LTD and SmithKline Beecham Corp., d/b/a
GlaxoSmithKline v. Teva Pharmaceuticals USA, Inc.*, Civil Action No. 05-197 (D. Del.)

Dear Karen:

I am writing in response to Teva's Notice of Deposition to Plaintiffs GlaxoSmithKline pursuant to Rule 30(b)(6) of the Federal Rules of Civil Procedure ("Notice"). GSK's objections to the Notice ("Objections") are enclosed.

Subject to its Objections, GSK designates the following witnesses to testify as its corporate representatives:

- REDACTED will testify about Topic Number 1 with respect to the '808 patent.

REDACTED

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REDACTED

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REDACTED

GSK has not yet identified corporate representatives to testify about the remaining topics on which GSK has agreed to produce a witness, but we will get back to you as soon as that information is available. In the same vein, please let me know as soon as possible which individual(s) Teva will designate to testify about the remaining topics in the 30(b)(6) notice GSK served on Teva.

Wilmer Cutler Pickering Hale and Dorr LLP, 2445 M Street, NW, Washington, DC 20037

Baltimore Beijing Berlin Boston Brussels London Munich New York Northern Virginia Oxford Palo Alto Waltham Washington

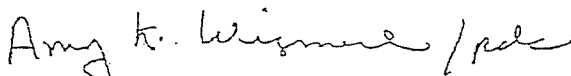
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WILMERHALE

Karen M. Robinson
May 2, 2006
Page 2

Please contact me at your earliest convenience to confirm the deposition dates referenced above.

Sincerely,


Amy K. Wigmore

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SMITH KLINE & FRENCH
LABORATORIES LIMITED and
SMITHKLINE BEECHAM
CORPORATION d/b/a
GLAXOSMITHKLINE,

Plaintiff,

v.

TEVA PHARMACEUTICALS USA, INC.,

Defendant.

Civil Action No. 05-197-GMS

**PLAINTIFFS' OBJECTIONS TO
NOTICE TO TAKE RULE 30(b)(6) DEPOSITION**

Pursuant to Federal Rules of Civil Procedure 26 and 30, the Plaintiffs Smith Kline & French Laboratories Limited and SmithKline Beecham Corporation, d/b/a GlaxoSmithKline (collectively, "GSK") hereby state their objections to the Notice of Deposition to Plaintiffs GlaxoSmithKline ("Notice"), served by the Defendant Teva Pharmaceuticals USA, Inc.'s ("Teva") on April 5, 2006.

GENERAL OBJECTIONS

Each of GSK's responses, in addition to being subject to any specifically stated objections, is subject to and incorporates the following General Objections. The assertion of the same, similar, or additional objections, or a partial response to an individual topic specified in the Notice (collectively the "Topics"), does not waive any of GSK's General Objections.

1. GSK incorporates by reference, as if fully set forth herein, the General Objections that GSK has made in its Responses and Objections to Defendant's First Set of Requests for

Production of Documents and Things.

2. GSK objects to the Notice to the extent that it seeks information protected from disclosure by the attorney-client privilege, the attorney work product doctrine, or any other applicable privilege, protection, or immunity. No person will be designated to testify about information subject to such privilege, protection, or immunity.

3. GSK objects to the Notice to the extent it seeks duplicative information already requested by, or more appropriately obtained through, other discovery mechanisms.

4. GSK objects to the Notice to the extent it seeks information that is confidential and/or proprietary. GSK will designate person(s) to testify about information that is confidential and/or proprietary subject to the Protective Order entered in this case.

5. None of the objections or responses set forth below is an admission of the relevance or admissibility of any information, the truth or accuracy of any statement or characterization contained in the Notice, the existence of information that is responsive to a Topic, or the existence of any person(s) with knowledge about information that is responsive to a Topic.

SPECIFIC OBJECTIONS AND RESPONSES

Topic No. 1

The facts and circumstances regarding the conception and reduction to practice (if any) of the claims of the Patents-in-Suit and the development of the subject matter claimed in United States Patents Nos. 4,452,808 ("the '808 patent") and 4,824,860 ("the '860 patent") (collectively, "Patents-in-Suit") from conception up until the time of the filing of the respective applications from which the Patents-in Suit issued.

Response: GSK objects to this Topic to the extent that it calls for a legal conclusion and to the extent it calls for privileged attorney-client communications and/or work product. GSK further objects to this Topic as overly broad, unduly burdensome, and not reasonably calculated to lead to discoverable evidence to the extent it encompasses the conception and reduction to practice of claims not being asserted in this action. Subject to and without waiving the foregoing General and Specific Objections, GSK will designate one or more persons with knowledge to testify at a mutually agreeable time about the conception and reduction to practice of the claims of the '808 and '860 patents being asserted in this action.

Topic No. 2

All testing, studies or analysis of compounds covered by the claims of the Patents-in-Suit performed after the applications from which the Patents-in-Suit issued were filed

Response: GSK objects this Topic to the extent that it is overly broad, is not reasonably calculated to lead to discoverable evidence, and calls for privileged attorney-client communications and/or work product. This Topic is overly broad, unduly burdensome, and not reasonably calculated to lead to discoverable evidence to the extent it: (a) covers "all" testing, studies or analysis; (b) covers testing, studies, or analysis post-dating the filing of the '860 patent application; and (c) encompasses testing, studies, or analysis of compounds other than ropinirole hydrochloride. Subject to and without waiving the foregoing General and Specific Objections, GSK will designate one or more persons with knowledge to testify at a mutually agreeable time about testing, studies, or analysis of ropinirole hydrochloride conducted by GSK up until the filing date the '860 patent application.

Topic No. 3:

All testing, studies, or analysis of compounds covered by the claims of the United States Patent No. 4,314,944 ("the '944 patent").

Response: GSK objects to the Topic as overly broad, unduly burdensome, and not reasonably calculated to lead to discoverable evidence to the extent that it: (a) covers "all" testing, studies, or analysis; (b) relates to a compound and a patent that is not at issue in this action. GSK also objects to this Topic to the extent it calls for privileged attorney-client communications and/or work product. GSK will not designate a witness to testify about this topic.

Topic No. 4

The facts and circumstances surrounding the decision to file a new drug application for ropinirole as a treatment for Parkinson's Disease including the basis for deciding to pursue the ropinirole compound instead of other compounds covered by either the '808 patent or the '944 patent.

Response: GSK objects to the Topic to the extent that it is irrelevant, overly burdensome, not reasonably calculated to lead to discoverable evidence, and calls for privileged attorney-client communications and/or work product. Subject to and without waiving the foregoing General and Specific Objections, GSK will designate one or more persons with knowledge reasonably identified as responsive to this Topic to testify at a mutually agreeable time.

Topic No. 5

The facts and circumstances related to any claim that the invention(s) claimed in the Patents-in-Suit are non-obvious based on their "commercial success" as defined in Graham v. John Deere Co., 383 U.S. 1 (1966).

Response: GSK objects to the extent that this Topic calls for a legal conclusion and/or expert testimony. Subject to and without waiving the foregoing General and Specific Objections, GSK will designate one or more persons with knowledge reasonably identified as responsive to this Topic to testify at a mutually agreeable time.

Topic No. 6

The facts and circumstances related to the market for ropinirole from the product launch until present.

Response: GSK objects to the extent that this Topic calls for expert testimony. Subject to and without waiving the foregoing General and Specific Objections, GSK will designate one or more persons with knowledge reasonably identified as responsive to this Topic to testify at a mutually agreeable time.

Topic No. 7

Customers, revenues, and profits related to sales of ropinirole for treating Parkinson's Disease.

Response: GSK objects to the extent that this Topic is overly broad and to the extent it calls for expert testimony. GSK further objects that this Topic is overly burdensome and not

reasonably calculated to lead to discoverable evidence to the extent it covers the identities of specific customers. Subject to and without waiving the foregoing General and Specific Objections, GSK will designate one or more persons with knowledge reasonably identified as responsive to this Topic (aside from specific customer identities) to testify at a mutually agreeable time.

Topic No. 8

Expenses and costs related to sales of ropinirole for treating Parkinson's Disease.

Response: GSK objects to the extent that this Topic is overly broad and to the extent it calls for expert testimony. Subject to and without waiving the foregoing General and Specific Objections, GSK will designate one or more persons with knowledge reasonably identified as responsive to this Topic to testify at a mutually agreeable time.

Topic No. 9

Information related to customer purchase decisions related to ropinirole for treating Parkinson's Disease including any survey data.

Response: GSK objects to the extent that this Topic is overly broad and to the extent it calls for expert testimony. GSK further objects to this Topic to the extent it calls for information outside GSK's possession, custody, and control. Subject to and without waiving the foregoing General and Specific Objections, GSK will designate one or more persons with knowledge reasonably identified as responsive to this Topic to testify at a mutually agreeable time.

Topic No. 10

The facts and circumstances related to any assertion of secondary considerations of non-obviousness (as defined in Graham v. John Deere Co., 383 U.S. 1 (1966)) other than commercial success including any assertion of failure of others, unexpected results, or long felt need.

Response: GSK objects to the extent that this Topic calls for a legal conclusion and/or expert testimony. Subject to and without waiving the foregoing General and Specific Objections, GSK will designate one or more persons with knowledge reasonably identified as responsive to this Topic to testify at a mutually agreeable time.

Topic No. 11

All tests, analysis and studies of the compounds claimed in claim 1 of the '808 patent in which " R^1 , R^2 , or R^3 ," is a C_{1-4} lower alkyl."

Response: GSK objects this Topic to the extent that it calls for privileged attorney-client communications and/or work product. GSK further objects to this Topic as overly broad, unduly burdensome, and not reasonably calculated to lead to discoverable evidence to the extent it: (a) covers "all" tests, analysis and studies; and (b) relates solely to compounds other than ropinirole hydrochloride. GSK will not designate a witness to testify about this Topic.

Topic No. 12

All tests, analysis and studies of the compounds claimed in claim 1 of the '808 patent where "R" is anything other than "di-n-propylamino."

Response: GSK objects this Topic to the extent that it calls for privileged attorney-client communications and/or work product. GSK further objects to this Topic as overly broad, unduly burdensome, and not reasonably calculated to lead to discoverable evidence to the extent it: (a) covers "all" tests, analysis and studies; and (b) relates to compounds other than ropinirole hydrochloride. Subject to and without waiving the foregoing General and Specific Objections, GSK will designate one or more persons with knowledge to testify at a mutually agreeable time about testing, studies, or analysis of ropinirole hydrochloride conducted by GSK up until the filing date the '860 patent application

Topic No. 13

All tests, analysis and studies of the compounds described in claim 1 of the '860 patent in which "R³," is a "hydroxy."

Response: GSK objects this Topic to the extent that it calls for privileged attorney-client communications and/or work product. GSK further objects to this Topic as overly broad, unduly burdensome, and not reasonably calculated to lead to discoverable evidence to the extent it: (a) covers "all" tests, analysis and studies; and (b) relates solely to compounds other than ropinirole hydrochloride. GSK will not designate a witness to testify about this topic.

Topic No. 14

All attempts to develop methods of treatment using compounds claimed in the '808, '860 or '944 patents for indications other than Parkinson's Disease.

Response: GSK objects this Topic to the extent that it calls for privileged attorney-client communications and/or work product. GSK further objects to this Topic as overly broad, unduly

burdensome, and not reasonably calculated to lead to discoverable evidence to the extent it: (a) covers "all attempts" to develop methods of treatment; and (b) encompasses compounds and claims other than those at issue in this lawsuit. Subject to and without waiving the foregoing General and Specific Objections, GSK will designate one or more persons with knowledge to testify at a mutually agreeable time about GSK's efforts to develop ropinirole hydrochloride for indications other than Parkinson's Disease.

Topic No. 15

Any opinions, analyses, or evaluations of the claim scope, validity, enforceability or potential infringement of the Patents-in-Suit.

Response: GSK objects to this Topic because it directly calls for privileged attorney-client communications and/or work product. GSK will not designate a witness to testify about this Topic.

Topic No. 16

All documents and things related to the foregoing topics.

Response: GSK objects to this Topic as duplicative of previous discovery, overly broad, unduly burdensome, and not reasonably calculated to lead to discoverable evidence. GSK further objects to this Topic to the extent calls for privileged attorney-client communications and/or work product. GSK incorporates by reference herein its responses to Topics 1 through 15 above. GSK will not designate a witness to testify about this Topic.

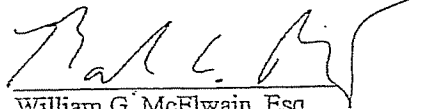
Topic No. 17

All persons known to have knowledge of the foregoing topics other than knowledge derived from involvement in this lawsuit.

Response: GSK objects to this Topic as duplicative of previous discovery, overly broad, and unduly burdensome, and not reasonably calculated to lead to discoverable evidence. GSK further objects to this Topic to the extent calls for privileged attorney-client communications and/or work product. GSK incorporates by reference herein its responses to Topics 1 through 15 above. GSK will not designate a witness to testify about this Topic.

SMITH KLINE & FRENCH LABORATORIES
LIMITED AND SMITHKLINE BEECHAM
CORPORATION, D/B/A GLAXOSMITHKLINE

By their attorneys,



William G. McElwain, Esq.

Henry N. Wixon, Esq.

Amy K. Wigmore, Esq.

Michael Gordon, Esq.

Mark L. Rienzi, Esq.

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Dated: ~~April~~ ^{May} 1, 2006
MAJ

REDACTED

EXHIBIT G

REDACTED

REDACTED

EXHIBIT H

REDACTED

EXHIBIT I

79287-54-0; 7x, 79287-59-5; 7s, 79287-34-6; 7t, 79290-47-4; 7u, 101712-51-0; 7v, 101712-52-1; 7w, 101712-53-2; 7z, 101712-54-3; 7y, 101712-55-4; 7z, 101712-56-5; 7aa, 101712-57-6; 7bb, 101712-58-7; 7cc, 101712-59-8; 7dd, 101712-60-1; 7ee, 79287-60-8; 7ff, 79290-50-9; 7gg, 101712-61-2; 7hh, 79290-49-6; 7ii, 101712-62-3; 7jj, 101712-63-4; 7kk, 101712-64-5; 7ll, 79290-48-5; (X = H), 90-43-7; 9 (X = 4-Cl), 64181-76-8; 10 (X = 4-Cl), 79287-41-5; 10 (X = H), 56837-38-6; 11 (X = 4-Cl), 79287-36-8; 11 (X = H), 19434-42-5; 12 (X = 4-OCH₃), 122-84-9; 12 (X = 2-OCH₃), 5211-62-1; 12 (X = 2,5-(OCH₃)₂), 14293-24-4; 12 (X = 3,4-(OCH₃)₂), 778-93-8; 12 (X = 4-CH₃), 2036-88-8; 12a (X = 4-Cl), 5585-88-8; 12a (X = 3-Cl), 14123-60-5; 12a (X = 2-Cl), 6305-95-9; 12b, 5097-32-1; 12c (X = 2-CF₃), 21235-67-8; 12c (X = 4-CF₃), 713-45-1; 12c (X = 3-CF₃), 21906-39-8; 12d, 770-39-8; 12e, 101712-18-9; 12f, 3374-50-2; 12g, 6304-16-1; 12h, 6302-03-0; 12i, 6302-02-9; 12j, 459-03-0; 12k, 1737-19-5; 12l, 2336-82-0; 12m, 101712-19-0; 12n, 101712-20-3; 12o, 19225-88-6; 12p, 88356-92-7; 13 (X = H, amine),

19434-42-5; 13a, 85841-96-9; 13a (amine), 79287-36-8; 13b, 79287-43-7; 13c, 79287-42-6; 13d, 79287-45-9; 13e, 79287-46-0; 13f, 79287-44-8; 13g, 79287-48-2; 13h, 53801-83-8; 13i, 23837-81-2; 13j, 101712-24-7; 13k, 31965-41-0; 13l, 101712-25-8; 13m, 101712-26-9; 13n, 101769-44-8; 13o, 101712-27-0; 13p, 69571-26-2; 13q, 33400-82-7; 13r, 79287-47-1; 13s, 101712-28-1; 13t, 101712-29-2; 13u, 101712-30-5; 13v, 101712-31-6; 13w, 101712-32-7; 13x, 101759-45-9; 4-CH₃C₆H₄C₆H₄OCH₃-2, 53824-28-0; 2-IC₃H₇OCH₃, 529-28-2; 4-CH₃C₆H₄I, 637-87-8; 4-FC₆H₄CH₂CO₂H, 405-50-5; 2-F₃CC₆H₄CH₂CO₂H, 3038-48-0; (E)-2-F₃CC₆H₄CH=CH-C(OCH₃)CH₃, 101712-21-4; (Z)-2-F₃CC₆H₄CH=CH-C(OCH₃)CH₃, 101712-22-5; C₆F₅CHO, 659-37-2; C₆NH₂CH₂, 79-24-3; C₆F₅C₆H₄-C(ND₂)CH₃, 101712-23-6; CH₃O(CH₂)₂OCHCl, 3970-21-6; modafinil, 86-42-0; modafinil N-oxide, 1245-23-7; cycloquin, 14594-33-3; cycloquin N-oxide, 101712-96-3; 4-methylpyridine, 103-89-4; sodium nitromalonalddehyde, 34461-00-2; 4,7-dichloroquinoline, 86-98-6; 4,7-dichloroquinoline N-oxide, 1077-74-3.

Syntheses and in Vitro Evaluation of 4-(2-Aminosthyl)-2(3H)-indolones and Related Compounds as Peripheral Prejunctional Dopamine Receptor Agonists

Robert M. DeMarinis,* Gregory Gallagher, Jr., Ralph F. Hall, Robert G. Franz, Charles Webster, William F. Huffman, Mark S. Schwartz, Carl Kaiser, Stephen T. Rose, James W. Wilson, and Paul Hieble¹

Departments of Medicinal Chemistry and Pharmacology, Research and Development Division, Smith Kline & French Laboratories, Philadelphia, Pennsylvania 19101. Received May 17, 1985

A series of (β-aminosthyl)indolones and related compounds was synthesized and evaluated in vitro as peripheral prejunctional dopaminergic agonists in the field-stimulated isolated perfused rabbit ear artery. 4-[2-(Di-n-propylamino)ethyl]-7-hydroxy-2(3H)-indolone (26) was the most potent compound (ED₅₀ = 2 ± 0.3 nM) tested, while the related secondary amine 24 and the des-OH derivatives 23 and 34 were only slightly less potent. 4-Methoxybenzeneethanamine and 2-methyl-3-nitrophenylacetic acid were employed as starting materials for the synthesis of the 4-(β-aminosthyl)indolones. The ring-opened 3-acylamino analogues 46 and 47 were prepared via nitration of the phenethylamines 43 derived from 4-methoxyphenylacetic acid. The inactive isomeric indolones 38, 39, and 41 were derived from 4-nitrobenzeneethanamine and from indolone-6-acetic acid (15).

During the past decade, evidence has accumulated to show that there are two distinct dopamine receptors in peripheral tissues. The peripheral postjunctional (D₂) receptor, located primarily in specific vascular beds such as the renal, mesenteric, and coronary arteries, mediates vasodilation.¹ The existence of this receptor was first suggested by in vivo studies showing dopamine-induced increases in renal blood flow in the dog.² This vascular D₂ receptor closely resembles the adenylate cyclase linked dopamine receptor found in the central nervous system.³

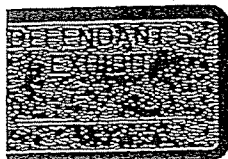
Recently, Langer discovered that activation of a dopaminergic receptor located on sympathetic nerve terminals in the perfused cat spleen would inhibit the release of neurotransmitter evoked by nerve stimulation.⁴ Subsequent studies have shown this prejunctional receptor to be present on terminals of many, but not all, sympathetic nerves, and although activation of this dopamine receptor has similar effects to activation of prejunctional α₂-adrenoceptors, these two neuroinhibitory receptors are pharmacologically distinct.⁵ The peripheral prejunctional dopamine receptor, designated D₂ by most investigators, is sensitive to dopamine and apomorphine at nanomolar concentrations and appears not to be coupled to adenylate cyclase. Much higher concentrations of dopamine, in the micromolar range, are required to activate D₁ receptors, and apomorphine acts as a weak partial agonist.⁴ In addition, D₁ and D₂ receptors can be differentiated with selective antagonists. The *l* enantiomer of sulpiride preferentially blocks the D₂ receptor, and the recently

discovered benzazepine derivatives SCH23390⁶ and SK&F 83566⁷ are highly selective for the D₁ subtype.

Stimulation of peripheral D₂ receptors is likely to be of therapeutic benefit in the treatment of cardiovascular disorders characterized by inappropriately high sympathetic tone. By inhibition of neurotransmitter release from the cardiac sympathetic nerve terminals, a D₂ agonist should attenuate the increase in cardiac work induced by exercise, stress, or any other stimulus that results in increased sympathetic drive. An additional benefit would be expected from concurrent inhibition of transmitter release from vascular sympathetic terminals, which would limit increases in vascular resistance and lower cardiac afterload. These sympathoinhibitory actions should be proportional to the degree of sympathetic activation; therefore a peripheral D₂ agonist should have little effect during intervals of low stress when sympathetic drive is low.

- (1) Brodde, O. E. *Life Sci.* 1982, 31, 259-306.
- (2) Goldberg, L. L.; Semmervilla, P. F.; McNay, J. L. *J. Pharmacol. Exp. Ther.* 1958, 163, 188-197.
- (3) Kebabian, J. W.; Carne, D. B. *Nature (London)* 1979, 277, 93-95.
- (4) Langer, S. Z. *Biochem. Pharmacol.* 1974, 23, 1793-1800.
- (5) Dubocovich, M. L.; Langer, S. Z. *J. Pharmacol. Exp. Ther.* 1980, 212, 144-152.
- (6) Hilditch, A.; Drew, G. M.; Naylor, R. M. *Eur. J. Pharmacol.* 1984, 97, 333-334.
- (7) Berkowitz, B. A.; Zabko-Potapovich, B.; Sherman, S.; Hieble, J. F.; Weinstein, J.; Ohlstein, E. H. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* 1984, 43, 743.

*Department of Pharmacology.

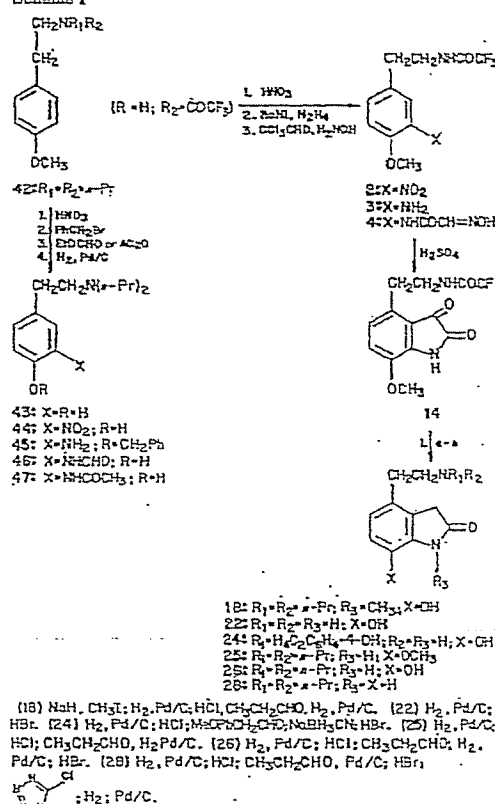


A number of different chemical structures have demonstrated preferential agonist activity at peripheral prejunctional D_2 vis-à-vis postjunctional D_1 receptors. These include for example alkylated derivatives of dopamines such as di-*n*-propyldopamine and *n*-propyl-*n*-butyldopamine; cyclized dopamine derivatives of the 2-aminotetralin series and apomorphine; ergot alkaloids such as bromocriptine and its simplified derivatives like LY141865.⁷ Our work in the area of dopamine agonists has for a number of years been centered on chemistry within a series of catechol-containing 3-benzazepines. This has resulted in the discovery of agonists that act at both peripheral pre- and postjunctional dopaminergic sites,⁹ as well as agents that act more selectively at postjunctional sites.¹⁰ Our interest in dopaminergic agonists has more recently focused on the identification of a selective peripheral D_2 agonist that is not a catechol and that also does not contain the basic chemical framework of the ergots or ergolines. We believed that a potent and selective peripheral D_2 agonist free of the limiting side effects related to the presence of an ergot structure or catechol would be a useful sympatholytic drug for cardiovascular therapy.

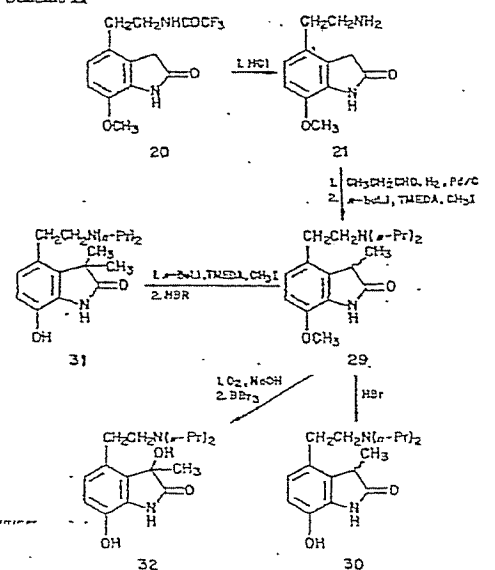
Our interest in the indolones was stimulated by the well-recognized prejunctional D_2 receptor agonist activity of certain ergot and ergoline derivatives including bromocriptine, lysergic acid diethylamide (LSD), lisuride, pergolide, and lergotril.¹¹ We postulated, as others have done,^{12,13} that the indolethanesamine fragment of the ergoline ring system was primarily responsible for the presynaptic dopaminergic receptor agonist activity of these compounds. By analogy with the reported active metabolites of the ergoline agonists,¹²⁻¹⁵ we speculated that oxidative metabolism of the less complex indolethanesamines might lead to indolones of the kind described in this paper. The active ergolines were attractive models since they offered clues to the discovery of simpler non-catechol structures that might exhibit high presynaptic D_2 receptor selectivity.

On the basis of this hypothesis, we have synthesized and evaluated for sympatholytic activity a series of 4-(2-aminomethyl)indolones. We have recently communicated the syntheses and prejunctional dopaminergic activity of two of these compounds.^{16,17} This paper describes in greater detail the syntheses of these agents and the preparation of a series of analogues related to them. All of the

Scheme I



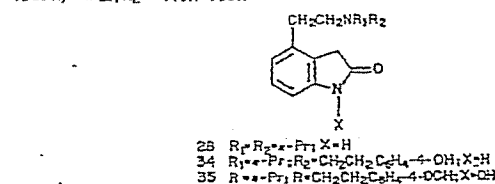
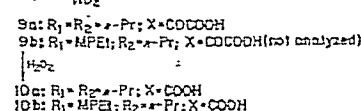
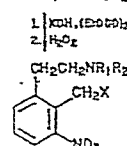
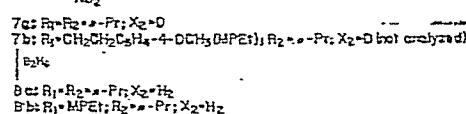
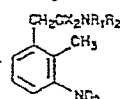
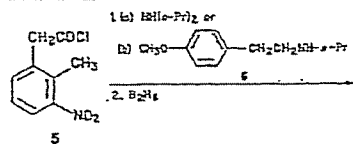
Scheme II



- (8) For a comprehensive review of this area, see: Keiser, C.; Jain, T. *Med. Res. Rev.* 1985, 5, 145 and references therein.
 (9) Blumberg, A. L.; Hieble, J. P.; McCafferty, J.; Hahn, R. A.; Smith, J., Jr. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* 1982, 41, 1845 (Abstr).
 (10) Weinstein, J.; Wilson, J. W.; Leidl, D. L.; Brash, C. K.; Pfeiffer, F. R.; Kuo, G. Y.; Holden, K. G.; Yim, N. C. F.; Hahn, R. A.; Wendell, J. R., Jr.; Tobin, A. J.; Setlar, P. E.; Sarau, H. M.; Ridley, P. T. *J. Med. Chem.* 1980, 23, 973-5.
 (11) Kornfeld, E. G.; Bach, N. J.; Titus, R. D.; Nichols, C. L.; Clemens, J. A. *Acta Pharm. Suec.* 1983, Suppl. 2, 83-97. *Proceedings of the Symposium on Dopamine Agonists, Structure-Activity Relationships, Clinical Aspects, Carlsberg, E. A., Nilsson, J. L. G., Eds.; Sweden Pharm. Press: Stockholm, 1983; Vol. 2.*
 (12) Cannon, J. G. *Bioass.* 1973, 20, 87-94.
 (13) Cannon, J. G.; Lee, T.; Hahn, M.; Kouns, J.; Lang, J. P. *J. Med. Chem.* 1984, 27, 388-389.
 (14) Parli, J. C.; Schmidt, B.; Shear, C. J. *Biochem. Pharmacol.* 1978, 27, 1405-1408.
 (15) Siddik, Z. H.; Barnes, R. D.; Dring, L. G.; Smith, R. L.; Williams, R. T. *Biochem. Pharmacol.* 1973, 23, 3083-3101.
 (16) Huffman, W. F.; Hall, R. F.; Grant, J. A.; Wilson, J. W.; Hieble, J. P.; Helm, R. A. *J. Med. Chem.* 1983, 26, 933-935.
 (17) Callaghan, G., Jr.; Lavanchy, P. G.; DeMarinis, R. M.; Wilson, J. W.; Hieble, J. P. *J. Med. Chem.* 1985, 28, 1633-1638.

Synthesis of 4-(2-Aminoethyl)-2(3E)-indolones

Scheme III



final targets (Table IV) have been evaluated in vitro for their ability to stimulate peripheral presynaptic dopaminergic receptors by using as a screening procedure measurement of the inhibition of electrically stimulated neurotransmission in the isolated perfused rabbit ear artery.¹⁸

Chemistry. With the exception of 33-35, the 4-(aminoethyl)indoles included in Table I were derived from commercially available 4-methoxybenzoesulfonamide as outlined in Schemes I and II. Compounds 33-35 were prepared from 2-methyl-3-nitrophenylacetic acid as shown in Scheme III. Compound 23 was prepared via Scheme III but was also obtained by hydrolysis of the phenyltetrazole ether 27 (Table I). The isomeric indolones 37-39 (Table II) were obtained from *N*-[2-(4-aminophenyl)ethyl]-2,2,2-trifluoroacetamide (11) by utilizing the Sandmeyer isatin synthesis (Scheme IV), and 6-[2-(di-n-propylamino)ethyl]indolone (41) was elaborated as outlined in Scheme V, from the known indolone-6-acetic acid (13). The ring-opened 3-acylamino analogues 46 and 47 (Table III) were prepared from commercially available 4-methoxyphenylacetic acid by using the procedures outlined in Scheme I.

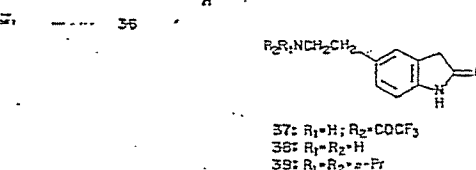
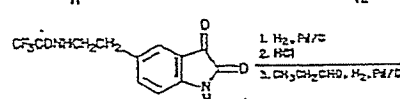
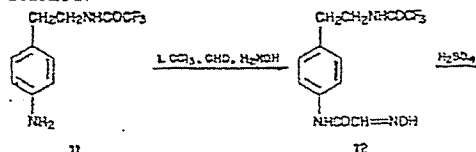
Biological Results

Compounds 22, 26, and 28 (Tables I and IV) are potent inhibitors of the constrictor response of the perfused rabbit

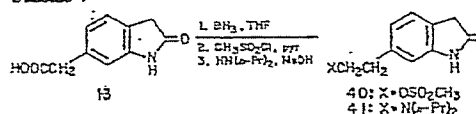
(18) Steinland, O. S.; Hieble, J. P. *Science* 1978, 199, 443-445.

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Scheme IV



Scheme V



ear artery (REA) to electrical field stimulation, and this effect is competitively antagonized by the dopaminergic receptor antagonist (*S*)-sulpiride. Our data show that the pharmacological effects of 26 and 28 are mediated primarily through activation of peripheral presynaptic D_2 receptors, since neither 26 nor 28 is able to stimulate or block the dopamine-sensitive adenylyl cyclase of rat caudate at concentrations up to 10^{-4} M and neither causes the stimulation of motor activity in rats at doses up to 1 mg/kg iv.¹⁹⁻²³ On the other hand, compound 22 does stimulate the cyclase significantly at 10^{-4} M, and this may be indicative of an ability, albeit weak, to activate postsynaptic D_1 receptors. We believe that the potency of 26 in the REA assay coupled with its lack of effects associated with activation of postsynaptic D_2 receptors is additional evidence of significant differences in peripheral pre- and postsynaptic receptors.

Comparison of the in vitro potency of 22 and 26 with the catechol standards DA and *N,N*-di-n-propyldopamine (DPDA) suggests equivalency of the lactam unit and the 3-OH of DA and DPDA in terms of receptor recognition. Such a hypothesis is supported in part by the significant in vitro activity observed with the des-OH compounds 28 and 34 (Tables I and IV) and the loss of activity observed with the isomeric indolones 38, 39, and 41 (Tables II and IV). It is of interest that the des-OH indolones 28 and 34 show in vitro potencies in the REA assay in the range of DA and DPDA, since the phenolic derivative *N,N*-di-n-

(19) Sulpiride, A. G.; Fowler, P. J.; Hieble, J. P.; Gallagher, G.; Wilson, J. W.; DeMarinis, R. M. *Pharmacologist* 1984, 26, 174 (Abstr.).

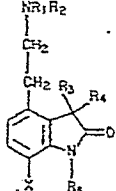
(20) Zeld, R. L.; Hieble, J. P.; DeMarinis, R. M.; Wilson, J. W. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* 1984, 43, 1020 (Abstr.).

(21) Hieble, J. P.; Jarvey, G. A.; Gruber, R. H.; Sarau, H. M.; Felsy, J. J.; Wilson, J. W.; DeMarinis, R. M. *Pharmacologist* 1983, 25, 162 (Abstr.).

(22) Detailed biological characterization of compounds 25 and 28 will be reported in forthcoming manuscripts.

(23) Summers, G.; Dijkstra, D.; deVries, J. B.; Ham, A. S. *Neuro-Schmidberg's Arch. Pharmacol.* 1981, 316, 504-510.

Table I. 4-(2-Aminoethyl)indolones and Intermediates



compd	R ₁	R ₂	R ₃	R ₄	R ₅	X	formula ^a	scheme/ method ^b	mp, °C	solvent	yield, %
14	H	COCF ₃			H	OCH ₃	C ₁₂ H ₁₁ F ₃ N ₂ O ₂	I	235.5-236	EtOAc- hexane	64
15	H	COCF ₃			CH ₃	OCH ₃	C ₁₂ H ₁₁ F ₃ N ₂ O ₂	I	203-205	EtOH	64
16	H	COCF ₃	H		H	CH ₃ , OCH ₃	C ₁₄ H ₁₃ F ₃ N ₂ O ₂	I/A	185-187	EtOH-H ₂ O	46
17	H	H	H		H	CH ₃ , OCH ₃	C ₁₂ H ₁₁ N ₂ O ₂ HCl	I	235-237	EtOH	76
18	<i>n</i> -Pr	<i>n</i> -Pr	H		H	CH ₃ , OH	C ₁₇ H ₂₁ N ₂ O ₂ HBr	I/B, C	227-229	H ₂ O	57
19	H	COCF ₃			H	OCH ₃	C ₁₂ H ₁₁ F ₃ N ₂ O ₂ 0.5H ₂ O	I	163.5	EtOAc- hexane	85
20	H	COCF ₃	H		H	OCH ₃	C ₁₄ H ₁₃ F ₃ N ₂ O ₂ 0.5H ₂ O	I/A ^c	173-179	EtOAc-CH ₂ Cl ₂	73
21	H	H	H		H	OCH ₃	C ₁₂ H ₁₁ N ₂ O ₂ HCl	I	258-260.5	MeOH- EtOAc	91
22	H	H	H		H	OH	C ₁₂ H ₁₁ N ₂ O ₂ HBr	I/C	250 dec	48% HBr (H ₂ O)	83
23	H	H ₃ C-C ₆ H ₄ -4-	H		H	OCH ₃	C ₂₂ H ₂₁ N ₂ O ₂ HCl	I	258-260 dec	CH ₂ CN	22
24	H	H ₃ C-C ₆ H ₄ -4- OCH ₃	H		H	OH	C ₂₂ H ₂₁ N ₂ O ₂ HBr	I/C	313-315 dec	48% HBr (H ₂ O)	87
25	<i>n</i> -Pr	<i>n</i> -Pr	H		H	OCH ₃	C ₁₇ H ₂₁ N ₂ O ₂ HCl	I/B	231-234	CH ₂ CN	72
26	<i>n</i> -Pr	<i>n</i> -Pr	H		H	OH	C ₁₇ H ₂₁ N ₂ O ₂ HBr	I/C	252-254	MeOH- EtOAc	75
27	<i>n</i> -Pr	<i>n</i> -Pr	H		H	H	C ₁₇ H ₂₁ N ₂ O ₂ HCl	I	245-246	CH ₂ CN	55
28	<i>n</i> -Pr	<i>n</i> -Pr	H		H	H	C ₁₄ H ₁₃ N ₂ O ₂ HCl	I, III	241-243	CH ₂ CN	76, 78 ^d
29	<i>n</i> -Pr	<i>n</i> -Pr	H		CH ₃	OCH ₃	C ₁₄ H ₁₃ N ₂ O ₂ HCl	II	195-196	CH ₂ CN	68
30	<i>n</i> -Pr	<i>n</i> -Pr	H		CH ₃	OH	C ₁₄ H ₁₃ N ₂ O ₂	II/C	183-185	EtOAc	69
31	<i>n</i> -Pr	<i>n</i> -Pr	CH ₃		CH ₃	OH	C ₁₄ H ₁₃ N ₂ O ₂ HBr	II/C	210-212	CH ₂ CN	24
32	<i>n</i> -Pr	<i>n</i> -Pr	CH ₃		OH	OH	C ₁₇ H ₂₁ N ₂ O ₂ (0.4 M NaCl)	II	~120 dec	EtOAc-Et ₂ O	5
33	<i>n</i> -Pr	H ₃ C-C ₆ H ₄ -4- OCH ₃	H		H	H	C ₂₂ H ₂₁ N ₂ O ₂ HCl	III	166-168	CH ₂ CN	22
34	<i>n</i> -Pr	H ₃ C-C ₆ H ₄ -4- OH	H		H	H	C ₂₂ H ₂₁ N ₂ O ₂ HBr	III/C	175 dec	CH ₂ CN	74
35	<i>n</i> -Pr	H ₃ C-C ₆ H ₄ -4- OCH ₃	H		H	OH	C ₂₂ H ₂₁ N ₂ O ₂ 0.5H ₂ O HCl	III	196-197.5	CH ₂ CN	31

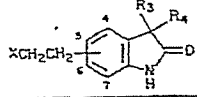
^a All compounds analyzed satisfactorily for C, H, and N unless indicated otherwise. ^b For methods A-C, see Experimental Section. I indicates that the procedure is described in the Experimental Section. ^c Preferably prepared directly from 14 by method A (71%). ^d Elemental analytical data was not obtained for this compound. ^e This compound was prepared via Scheme I (76%) and Scheme III (78%).

propyl-*m*-tyramine (DPMT), which has been reported to have *in vivo* central nervous system effects²³ but no activity in an *in vitro* assay for peripheral dopaminergic activity.²⁴

is also 1 order of magnitude less active in our REA assay than the nonphenolic indolones 28 and 34. Comparison of the assay results for compound 26 with those obtained for the ring-opened analogues 46 and 47 (Table III and IV) in the REA demonstrates a unique potency associated with the lactam ring of 26.

(24) Schmidt, M.; Imbs, J. L.; Giesen, R. M.; Schwartz, J. *Eur. J. Pharmacol.* 1982, 84, 61-70.

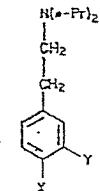
Table II. Isomeric (2-Aminoethyl)indolones and Intermediates



no.	R ³ , R ⁴	side-chain posit	X	formula ^a	scheme/method ^b	mp, °C	solvent	yield, %
36	O	5	NHCOCF ₃	C ₁₂ H ₁₀ F ₃ N ₂ O ₂	IV	194-194.5	EtOAc	82
37	H	5	NHCOCF ₃	C ₁₂ H ₁₀ F ₃ N ₂ O ₂	IV/A	203-204	AcOH-H ₂ O	83
38	H	5	NH ₂	C ₁₂ H ₁₂ N ₂ O-HCl	IV	276-280	MeOH	77
39	H	5	N(n-Pr) ₂	C ₁₅ H ₁₈ N ₂ O-HCl	IV/B	185.6-186.5	EtOH-Et ₂ O	70
40	H	6	OSO ₂ CH ₃	C ₁₁ H ₁₂ NO ₃ S	V	155.5-158	CH ₂ Cl ₂	78
41	H	6	N(n-Pr) ₂	C ₁₅ H ₁₈ (N ₂ O-HCl)-H ₂ O ^c	(phase change) 168	ppt from Et ₂ O	85	

^aSee footnote c, Table I. ^bSee footnote b, Table I. ^cN: calcd, 8.90; found, 8.47.

Table III. Ring Opened Analogues



compd	X	Y	formula	scheme/method ^c	mp, °C	solvent	anal.	yield, %
42	OCH ₃	H	C ₁₂ H ₁₂ NO	I	bp 113-115 °C (0.5 torr)	MeOH-Et ₂ O	C ₁₂ H ₁₂ N	75
43	OH	H	C ₁₂ H ₁₂ NO-HBr	I/C	154-155	MeOH-Et ₂ O	C ₁₂ H ₁₂ N	88
44	OH	NO ₂	C ₁₂ H ₁₀ N ₂ O ₃	I	60.5-61.5	EtOH-H ₂ O	C ₁₂ H ₁₀ N ₂ O	48
45	OCH ₃ Ph	NH ₂	C ₂₀ H ₁₈ N ₂ O-2HCl-2H ₂ O	I	107-110 dec	2-PrOH-Et ₂ O	C ₂₀ H ₁₈ N ₂ O	71
46	OH	NHCHO	C ₁₂ H ₁₂ N ₂ O-HCl-2H ₂ O	I	241.5-245.5	MeOH-Et ₂ O	C ₁₂ H ₁₂ N	63
47	OH	NHCOCH ₃	C ₁₂ H ₁₂ N ₂ O ₂ -HCl	I	164.5-165.5	MeOH-Et ₂ O	C ₁₂ H ₁₂ N	85

^aSee footnote b, Table I. ^bC: calcd, 76.55; found, 75.70. ^cH: calcd, 8.58; found, 8.65.

Table IV. Agonist Activity of 4-(Aminoethyl)indolones and Related Compounds at the Prejunctional Dopamine Receptor

compd	EC ₅₀ ^a , nM	N ^b	compd	EC ₅₀ ^a , nM	N ^b
18	>3000	4	34	23 ± 19	9
22	116 ± 43 ^c	8	38	>3000	2
24	53 ± 16	6	39	3000	2
25	>3000	2	41	>3000	2
26	2 ± 0.5 ^c	10	46	750 ± 188	5
28	100 ± 25 ^c	5	47	>10000	6
30	18 ± 3	11	DA ^c	73 ± 6 ^c	38
31	>3000	2	DPDA ^d	80 ± 17 ^c	13
32	218 ± 26	5	DPMT ^d	700 ± 209	5

^aConcentration SE required to inhibit by 50% the vasoconstrictor response to field stimulation in the isolated, perfused rabbit ear artery. See: Hieble, J. P.; Pendleton, R. G. *Neuryn-Schmiedebert's Arch. Pharmacol.* 1979, 309, 217. ^bNumber of determinations. ^cThis response competitively antagonized by (S)-sulpiride. ^dDA = dopamine, DPDA = N,N-di-n-propyldopamine, DPMT = N,N-di-n-propyl-m-tyramine. ^eCannon, J. G.; Hsu, F. L.; Long, J. P.; Flynn, J. R.; Cestell, B.; Naylor, R. J. *J. Med. Chem.* 1978, 21, 242. ^fWikström, H.; Lindberg, P.; Martinson, P.; Hjorth, S.; Carlsson, A.; Hackzell, U.; Svensson, U.; Nilsson, J. L. *J. Med. Chem.* 1978, 21, 864.

Starting from what we believed to be the intrinsic pharmacophore of the ergots, coupled with the knowledge of the presynaptic selectivity of alkylated dopamine analogues vis-à-vis dopamine itself, we have designed and synthesized a series of indolones of which several possess potent presynaptic dopaminergic agonist activity as their major pharmacological property. These compounds do not possess the complex ergot ring structure and do not contain the catechol moiety. Preliminary studies on the in vivo characterization of two of the most interesting congeners, 26 and 28, have been reported^{18,17} and more detailed

pharmacological characterization of these compounds will be published in future papers.

Experimental Section

Melting points were taken either in a Mel-Temp hot stage or in open capillary tubes with a Thomas-Hoover Unimelt apparatus and are uncorrected. When analyses are reported by symbols of the elements, results were within 0.4% of calculated values. Melting points, and yields are recorded for new compounds in Schemes I-III. IR spectra were recorded on a Perkin-Elmer Model 583 spectrophotometer and ¹NMR spectra were obtained on a Varian EM-390 spectrometer. Spectral data for all compounds were consistent with assigned structures. The C, H, and N analyses were carried out by the Analytical, Physical and Structural Chemistry Department of Smith Kline & French Laboratories.

N-[2-(4-Methoxyphenyl)ethyl]-2,2,2-trifluoroacetamide (1). To a cold solution of 50.0 g (0.331 mol) of 4-methoxybenzenethanemine in 500 mL of CH₂Cl₂ under an argon atmosphere was added dropwise with stirring a solution of 93.5 mL (0.664 mol) of (CF₃CO)₂O in 60 mL of CH₂Cl₂. After the mixture was stirred at room temperature for 1.5 h, the volatiles were removed, toluene was added and removed, and the residue was crystallized from 800 mL of 1:1 Et₂O-petroleum ether to give 65.8 (68.2%) of white needles of 1, mp 84.0 °C. An additional 16.6 g, mp 82.5-84.0 °C, was recovered from the filtrate to give a total yield of 72.4 g (83.4%). Anal. (C₁₄H₁₅F₃NO₂) C, H, N.

N-[2-(4-Methoxy-3-nitrophenyl)ethyl]-2,2,2-trifluoroacetamide (2). To a solution of 30.0 g (0.121 mol) of 1 in 254 mL of TFA under an argon atmosphere was added dropwise with stirring and cooling a solution of 7.5 mL (0.12 mol) of concentrated HNO₃ in 56 mL of TFA. After the mixture was stirred at room temperature for 2 h, the solvents were removed and the residue was dissolved in EtOAc, which was successively extracted with 5% HCl, dilute NaHCO₃, and brine and then dried (Mg SO₄, activated carbon). The mixture was filtered and the filtrate

concentrated. The resulting crude amber solid, 34.8 g (98%), was crystallized from 400 mL of 1:3 EtOAc-hexane to give 25.3 g (71.5%) of 2, mp 92.5–93.0 °C. A second crop, 4.59 g (13%), mp 90–92 °C, of 2 was obtained from the mother liquors. Anal. ($C_{11}H_{11}F_3N_2O_2$) C, H, N.

N-[2-(3-Amino-4-methoxyphenyl)ethyl]-2,2,2-trifluoroacetamide (3). To a mixture of 80 g of activated Raney nickel catalyst and a solution of 400 g (1.359 mol) of 2 in 4 L of EtOH was added dropwise with cooling and stirring under an argon atmosphere a solution of 200 mL (4.115 mol) of hydrazine hydrate in 2 L of EtOH. Stirring was continued at 15 °C for 2 h and 92 mL of HOAc was added dropwise to bring the pH to 7.0. The mixture was filtered and the filtrate treated with activated carbon. The carbon was removed, and the volatile solvents were evaporated in vacuo. The semisolid residue was triturated with EtOAc and the residual solid removed by filtration and washed with EtOAc. After extraction three times with brine, the EtOAc solution was dried ($MgSO_4$), filtered, and evaporated. The residue was dissolved in 1770 mL of Et₂O and 1000 mL of hexane was added. After cooling, 221.7 g of 3, mp 87–88 °C was obtained. A second crop, 52.2 g (total yield 76.3%), was recovered from the filtrate. Anal. ($C_{12}H_{13}F_3N_2O_2$) C, H, N.

N-[2-[3-(Hydroxylaminoacetyl)amino]-4-methoxyphenyl]ethyl]-2,2,2-trifluoroacetamide (4). A mixture of 44.5 g (0.17 mol) of 3, 940 mL of H₂O, and 11.5 mL (0.207 mol) of concentrated H₂SO₄ was combined with a mixture of 29.1 g (0.176 mol) of chloral hydrate, 87.5 g (0.533 mol) of hydroxylamine sulfate, and 240 mL of H₂O. This mixture was heated rapidly to reflux in an argon atmosphere and after 4 min of reflux was allowed to cool to room temperature. The crude solid product was filtered, washed with H₂O, and dried. The residue was dissolved in hot EtOAc, clarified with activated carbon, and diluted at reflux with hexane. Upon cooling, 27.5 g (50%) of 4, mp 195–197 °C, was obtained. A second crop 9.9 g, mp 192–195 °C (total yield 63%), was obtained from the filtrate. ¹H NMR ($Me_2SO-d_6/CDCl_3$) δ 2.62–3.62 (m, 4 H, CH₂), 3.61 (s, 3 H, OCH₃), 6.82 (d, 2 H), 7.53 (s, 1 H), 8.18 (s, 1 H (exch)), 8.90 (s, 2 H (exch)), 11.90 (s, 1 H (exch)). Anal. ($C_{12}H_{14}F_3N_4O_5$) C, H, N.

7-Methoxy-4-[2-(trifluoroacetamido)ethyl]isatin (14). One portion, 5.0 g (0.015 mol), of powdered 4 was added with stirring to 50 mL of concentrated H₂SO₄ under argon at 80 °C. Heating was continued for 6 min after solution was achieved. The reaction solution was poured over 500 g of cracked ice and the product was taken into EtOAc by two 200-mL extractions. The EtOAc solution was extracted with dilute aqueous NaHCO₃ and brine and then dried ($MgSO_4$). After removal of the $MgSO_4$, the solution was filtered through 200 g of silica gel and the filtrate evaporated to give 3.05 g of red crystalline 14: IR (KBr) 1750, 1735, 1705 cm^{-1} ; ¹H NMR ($Me_2SO-d_6/CDCl_3$) δ 3.08 (t, 2 H, CH₂), 3.50 (t, 2 H, CH₂), 3.99 (s, 3 H, OCH₃), 6.82 (d, 1 H, *J* = 9 Hz), 7.12 (d, *J* = 3 Hz, 1 H), 9.12 (m, 1 H (exch)).

7-Methoxy-1-methyl-4-[2-(trifluoroacetamido)ethyl]isatin (15). A mixture of 0.532 g (0.002 mol) of 14 and NaH, 0.058 g (0.0024 mol), in 10 mL of dry THF was treated with CH₃I, 1.14 g (0.008 mol), in three portions over a period of 2 days at room temperature. The reaction mixture was quenched with saturated aqueous NH₄Cl and extracted into 95:5 EtOAc-EtOH and crystallized from EtOH after removal of solvent; 0.43 g of 15: IR (Nujol) 1735, 1720, 1690 cm^{-1} ; ¹H NMR ($MeOH-d_4/CDCl_3$) δ 3.11 (t, *J* = 6 Hz, 2 H, CH₂), 3.48 (t, *J* = 6 Hz, 2 H, CH₂), 3.50 (s, 3 H, NCH₃), 3.92 (s, 3 H, OCH₃), 6.85 (d, *J* = 9 Hz, 1 H (Ar)), 7.17 (d, *J* = 9 Hz, 1 H (Ar)).

7-Methoxy-1-methyl-4-[2-(trifluoroacetamido)ethyl]-2-(3H)-indolone (16). A mixture of 0.430 g (0.0013 mol) of 15 and 0.22 g of 10% Pd/C catalyst in 20 mL of HOAc containing 0.2 mL of 70% perchloric acid was hydrogenated at 50 °C for 8 h. After removal of the catalyst and solvent, H₂O and EtOAc were added to the residue, and the mixture was brought to pH 7 with NaOAc. The EtOAc phase was separated and the solvent removed in vacuo. Crystallization of the pink solid residues from 90:10 H₂O-EtOH gave 0.19 g of 16 as orange needles: IR (KBr) 1720, 1690 cm^{-1} ; ¹H NMR ($MeOH-d_4/CDCl_3$) δ 2.75 (t, *J* = 6 Hz, 2 H, CH₂), 3.47 (s, 3 H, NCH₃), 3.51 (t, *J* = 5 Hz, 2 H, CH₂), 3.85 (s, 3 H, OCH₃), 6.81 (s, 2 H (Ar)).

This general procedure for the catalytic conversion of isatins to indolones has been used in the preparation of other compounds

(Tables I and II) and is designated method A.

4-(2-Aminoethyl)-7-methoxy-1-methyl-2(3H)-indolone Hydrochloride (17). A solution of 0.41 g (0.0013 mol) of 16 in 2.5 mL of EtOH and 5.4 mL of H₂O containing 1.5 mL of concentrated HCl was refluxed for 20 h under a N₂ atmosphere. The solution was taken to dryness in vacuo. The residue was triturated with CH₃CN and Et₂O and crystallized from EtOH to yield 0.25 g.

4-[2-(Di-*n*-propylamino)ethyl]-7-hydroxy-1-methyl-2-(3H)-indolone Hydrobromide (18). A solution of 0.180 g (0.0007 mol) of 17 in 30 mL of HOAc containing 0.128 g (0.0022 mol) of propionaldehyde and 85 mg of 10% Pd/C catalyst was hydrogenated at 50 °C and 45 psi for 7 h. The catalyst and solvent were removed, and the residue was dissolved in H₂O and made alkaline with Na₂CO₃. The free base was extracted into EtOAc. The EtOAc was removed in vacuo and the residue was refluxed under nitrogen with 3 mL of 48% HBr for 4 h. After removal of the HBr in vacuo, the residue was crystallized from H₂O to give 0.15 g of rust colored crystals: IR (KBr) 1672 cm^{-1} ; ¹H NMR (D_2O) δ 1.35 (t, 6 H, CCH₃), 2.10 (m, 4 H, CCH₂C), 3.05–3.64 (m, 9 H), 3.65 (s, 3 H, NCH₃), 7.19 (s, 2 H (Ar)).

The reductive alkylation procedure described in this experiment has been used for the preparation of other compounds (Tables I and II) and is designated method B. The ether cleavage procedure similarly has been used in other instances and is designated method C.

3,3-(Ethyleneedithio)-7-methoxy-4-[2-(trifluoroacetamido)ethyl]-2(3H)-indolone (19). A mixture of 23.9 g (0.076 mol) of 14 and 28.0 mL (0.32 mol) of ethanedithiol in 700 mL of anhydrous CH₂Cl₂ was stirred at room temperature under argon while 6.3 mL (0.051 mol) of freshly distilled boron trifluoride etherate was added. After stirring at room temperature for 16 h, an additional 1.0 mL (0.003 mol) of boron trifluoride etherate was added and stirring was continued for 7 h. The mixture was diluted with 1500 mL of CCl₄ and cooled overnight at –23 °C. The solid was removed and dissolved in EtOAc/Et₂O, and this solution was extracted with H₂O, aqueous NaHCO₃, and brine. After drying ($MgSO_4$) and treatment with activated carbon, the solvent was removed and the residue recrystallized from EtOAc-hexane; 19.7 g (67%) of 19. A second crop, 5.6 g (18%), was recovered from the filtrate.

7-Methoxy-4-[2-(trifluoroacetamido)ethyl]-2(5H)-indolone (20). To a partial solution of 1 g (0.0026 mol) of 19 in 10 mL of absolute EtOH under argon was added with stirring 8 g of Raney nickel catalyst in 50 mL of absolute EtOH. After the mixture was stirred for 2 h, the catalyst was removed and the solvent removed. The residue was dissolved in EtOAc and extracted with 3 N HCl, H₂O, 5% NaHCO₃, and brine. After drying ($MgSO_4$) and treatment with activated charcoal, the EtOAc was removed and the residue crystallized from EtOAc-hexane to yield 0.661 g (73%) of 20, mp 176–178 °C. A solution in EtOAc-CH₂Cl₂ was filtered through silica gel to give 540 mg; mp 178–179 °C; IR (KBr) 1735, 1690 cm^{-1} ; ¹H NMR ($CDCl_3$) δ 2.79 (t, 2 H), 3.49 (s, 2 H, CH₂CO), 3.60 (t, 2 H), 3.85 (s, 3 H, OCH₃), 6.76 (s, 2 H (Ar)), 7.56 (br s, 1 H (exch)).

4-(2-Aminoethyl)-7-methoxy-2(3H)-indolone (21). The amide 20, 28.0 g (0.093 mol), was hydrolyzed as described for the preparation 17 to give 20.4 g of copper-colored needles.

4-[2-[2-(*p*-Methoxyphenyl)ethyl]amino]ethyl]-7-methoxy-2(3H)-indolone Hydrochloride (23). 4-Methoxyphenylacetaldehyde was prepared by a modification of procedures described by Ben and Oishi²⁵ and by Hino and co-workers.²⁶ To a mixture of 5.0 g (0.0192 mol) of 21 and 0.88 g (0.016 mol) of KOH in 50 mL of MeOH was added with stirring 2.88 g (0.0192 mol) of the freshly distilled (bp 117–118 °C (9 mmHg)) 4-methoxyphenylacetaldehyde. To the resulting mixture was added 0.48 g (0.0073 mol) of sodium cyanoborohydride. After the mixture was stirred at room temperature for 3 days, an additional 1.0 g (0.0159 mol) of sodium cyanoborohydride was added and the pH was adjusted to 6.3. After the mixture was stirred an additional 4 h, H₂O was added and the pH adjusted to 12. The mixture was

(25) Ben, Y.; Oishi, T. *Chem. Pharm. Bull.* 1958, 6, 574–576.

(26) Hino, T.; Suzuki, T.; Nakagawa, M. *Chem. Pharm. Bull.* 1973, 21, 2785–2789.

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extracted three times with CH_2Cl_2 . The solvents were removed in vacuo, and the residual oil was dissolved in Et_2O and made acidic by the addition of ethereal HCl . The solid salt that precipitated was triturated with EtOAc and crystallized from CH_3CN to give 1.6 g of 23.

4-[2-(Di-n-propylamino)ethyl]-7-methoxy-3(R,S)-methyl-2(3H)-indolone Hydrochloride (29). The procedure of Kende and Hodges²⁷ was employed. To a cold solution (-78°C) of 2.18 g (0.0075 mol) of the free base of 25 in 50 mL of dry THF containing 2.3 mL (0.015 mol) of tetramethylethylenediamine under a nitrogen atmosphere were added 0.99 g (0.0155 mol) of cold n-butyllithium in hexane and then 2.13 g (0.015 mol) of CH_2I_2 . After 1 h the temperature was allowed to rise slowly (3.5 h) to room temperature. The reaction mixture was poured into a saturated aqueous NH_4Cl solution and the product extracted into Et_2O . After drying (MgSO_4), ethereal HCl was added to the Et_2O solution and the orange oil that separated was triturated repeatedly with CH_2Cl_2 . Recrystallization of the resulting granular solid from CH_3CN gave 1.74 g of 29: ^1H NMR (D_2O) δ 1.05 (t, 6 H, CH_3), 1.40 (d, 3 H, CH_3), 1.54-2.05 (m, 4 H), 2.70-3.60 (m, 10 H), 3.89 (s, 3 H, OCH_3), 6.92 (s, 2 H (Ar)).

3,3-Dimethyl-4-[2-(di-n-propylamino)ethyl]-7-hydroxy-2(3H)-indolone Hydrochloride (31). The alkylation procedure employed for the preparation of 29 was repeated with use of 0.61 g (0.002 mol) of the free base of 29 as the starting material. The crude product consisted of a mixture of 29 and the 7-methoxy derivative of 31. An alkaline suspension (dilute NaOH) of the crude product was stirred at room temperature in the open air for 18 h. After cooling, the pH was adjusted to 9 with concentrated HCl and the crude product was extracted into Et_2O . The desired intermediate was separated from the oxidation product of 29 (the methyl ether of 32) by chromatography on Baker 40- μm silica gel with use of 1:1 acetone-petroleum ether. Without further purification, this material was converted to the desired product 31 with 2 mL of 48% HBr by using method C: ^1H NMR (D_2O) δ 1.05 (t, 6 H, CH_3), 1.44 (s, 6 H, $\text{C}(\text{CH}_3)_2$), 1.59-2.04 (m, 4 H), 2.95-3.62 (m, 8 H), 6.89 (s, 2 H (Ar)).

3,7-Dihydroxy-4-[2-(di-n-propylamino)ethyl]-3-methyl-2(3H)-indolone (32). To a solution of 0.33 g (0.001 mol) of 29 in a mixture of 4 mL of MeOH and 5 mL of H_2O was added 0.5 mL of 40% NaOH . This reaction mixture was stirred in the open air at room temperature for 18 h and then diluted with ice, and the pH was adjusted to 2 with dilute HCl . After 30 min the pH was brought to 8.5 with dilute NaOH , and the aqueous phase was saturated with NaCl and extracted with EtOAc . The EtOAc extract was chromatographed on 40- μm Baker silica gel with 190:10:1 EtOAc - MeOH -concentrated NH_4OH to give 0.048 g of intermediate as the free base. A cold (-75°C) solution of 0.054 g (0.0032 mol) of this intermediate in 5 mL of dry CH_2Cl_2 was treated with 1.1 mL of 1 M BBR_3 in CH_2Cl_2 . The reaction was allowed to warm slowly to room temperature and was then stirred for 18 h. The solvent was removed in a stream of N_2 . Ice containing 2 drops of concentrated NH_4OH was added to the residue. The pH was adjusted to 2 with 3 N HCl and after 15 min readjusted to 8 with use of 10% NaHCO_3 . The aqueous phase was saturated with NaCl and exhaustively extracted with EtOAc . The EtOAc was removed in vacuo and the residual oil triturated with 1:1 Et_2O -petroleum ether to give 0.021 g of 32: ^1H NMR (CDCl_3) δ 1.05 (t, 6 H, CH_3), 1.55-2.02 (m, 4 H), 1.70 (s, 3 H, HOCH_2), 3.00-3.50 (m, 8 H), 6.98 (s, 2 H (Ar)); IR (KBr) 1721 cm^{-1} .

4-[2-(Di-n-propylamino)ethyl]-7-[(1-phenyl-1H-tetrazol-5-yl)oxy]-2(3H)-indolone Hydrochloride (27). A modification of the procedure of Teitel and O'Brien²⁸ was employed. A mixture of 3.43 g (0.0096 mol) of 25, 2.03 g (0.021 mol) of anhydrous K_2CO_3 , and 1.77 g (0.039 mol) of 5-chloro-1-phenyl-1H-tetrazole in 220 mL of acetone, 50 mL of DMF, and 10 mL of H_2O was refluxed for 18 h. The mixture was filtered, and after the filtrate was concentrated in vacuo, the residue was diluted with H_2O , saturated with NaCl , and extracted with Et_2O . After drying (MgSO_4), the ether solution was treated with ethereal HCl . The solid residue was triturated with Et_2O and crystallized from CH_3CN to give 3.8 g of white crystalline product: ^1H NMR ($\text{MeOH}-d_4$) δ 1.08

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(t, 6 H, CH_2CH_3), 1.61-2.09 (m, 4 H, CH_2CH_3), 2.95-3.57 (m, 10 H), 7.05 (d, 1 H (Ar)), 7.26 (d, 1 H (Ar)), 7.53-7.97 (m, 5 H (Ar)); IR (KBr) 1738, 1710 cm^{-1} .

4-[2-(Di-n-propylamino)ethyl]-2(3H)-indolone Hydrochloride (28) (via Scheme 1). A mixture of 2.64 g (0.00578 mol) of 27 and 1.49 g of 10% Pd/C catalyst in 200 mL of HOAc was hydrogenated for 20 h at 50 psi and 60°C . The catalyst was removed and the solution concentrated in vacuo. The residue was partitioned between $\text{H}_2\text{O}/\text{EtOAc}$ and acidified with dilute HCl . The aqueous phase was made alkaline (pH 8.5) with 10% NaOH . The product was extracted into $\text{EtOAc}/\text{Et}_2\text{O}$ and after drying (MgSO_4), this solution was treated with ethereal HCl to give a pale yellow crystalline product: ^1H NMR (CDCl_3 - $\text{MeOH}-d_4$) δ 1.05 (t, 6 H, CH_2CH_3), 1.53-2.08 (m, 4 H, CH_2CH_3), 2.95-3.50 (m, 10 H), 6.75-7.35 (m, 3 H (Ar)); IR (KBr) 1760, 1725, 1705 cm^{-1} .

2-(2-Methyl-3-nitrophenyl)-N,N-di-n-propylacetamide (7a). To 50.0 g (0.256 mol) of 2-methyl-3-nitrophenylacetic acid²⁹ was added dropwise with stirring 95 g (0.80 mol) of SOCl_2 . When gas evolution ceased, the solution was concentrated in vacuo, and several small portions of dry toluene were added and removed in vacuo. The residue was dissolved in 300 mL of toluene and added at 10°C to 600 mL of a 50:50 H_2O -toluene mixture containing 30 g (0.283 mol) of Na_2CO_3 . Di-n-propylamine, 301 g (0.30 mol), was added with cooling and slow stirring, and after 0.5 h the mixture was brought to room temperature and stirred for an additional hour. An additional 1.0 g (0.0094 mol) of Na_2CO_3 was added and the toluene phase was separated, washed with 5% Na_2CO_3 , 1.5 N HCl , and H_2O . After drying (MgSO_4), the solvent was removed and the thick residual oil was distilled in a Kugelrohr apparatus to give 64 g of product, bp 150°C (0.1 mmHg), which crystallized as long needles: mp $49-50^\circ\text{C}$; ^1H NMR (CDCl_3) δ 0.78-1.08 (m, 6 H, CH_2CH_3), 1.37-1.89 (m, 4 H, CH_2CH_3), 2.35 (s, 3 H, Ar CH_3), 3.19-3.45 (m, 4 H, NCH_2), 3.75 (s, 2 H, CH_2CO), 7.13-7.75 (m, 3 H (Ar)); IR (neat) 1641, 1525, cm^{-1} . Anal. ($\text{C}_{15}\text{H}_{21}\text{N}_2\text{O}_2$) C, H, N.

2-Methyl-3-nitro-N,N-di-n-propylphenethylamine (8a). To a solution of 155.74 g (0.560 mol) of 7a in 1250 mL of anhydrous THF was added dropwise 848 mL of 1.0 M borane in THF. The mixture was refluxed for 1 h, an additional 150 mL of 1.0 M borane-THF was added, and this solution was stirred overnight. Anhydrous MeOH was added cautiously and the solution was concentrated in vacuo. The residual syrup was warmed on a steam bath with 6 N HCl (200 mL) for 1 h and then cooled and made basic with 40% NaOH . The oily product was taken into Et_2O , washed with brine, concentrated in vacuo, and distilled in a Kugelrohr flask to yield 123.94 g (83%) of thick oil: bp $115-120^\circ\text{C}$ (0.1 mmHg); ^1H NMR (CDCl_3) δ 0.89 (t, 6 H, CH_2CH_3), 1.22-1.70 (m, 4 H, CH_2CH_3), 2.34-2.58 (m, 3 H), 2.42 (s, 3 H, Ar CH_3), 7.08-7.56 (m, 3 H (Ar)). Anal. ($\text{C}_{17}\text{H}_{25}\text{N}_2\text{O}_2$) C, H, N.

2-Nitro-6-[2-(N,N-di-n-propylamino)ethyl]phenylpyruvic Acid (9a). Absolute EtOH , 0.89 g (0.0193 mol), was added dropwise to freshly cut K metal, 0.75 g (0.019 mol), in anhydrous Et_2O under a nitrogen atmosphere. Diethyl oxalate, 2.77 g (0.019 mol), was added dropwise with stirring after the metal had dissolved. After 10 min, 5.03 g (0.019 mol) of 9 was added dropwise. After an additional 10 min of stirring, the dark purple solution was allowed to stand overnight. The solution was concentrated with a stream of N_2 and 100 mL of H_2O was added (pH 10). The solution was extracted with Et_2O , and after drying (MgSO_4), the ether was removed to provide 2.59 g of crude unreacted starting material 8a. The H_2O layer was diluted with 300 mL of H_2O and acidified to pH 1.5 with 3 N HCl . The tan precipitate was separated and crystallized from HOAc : 3.37 g (52%), mp $220-225^\circ\text{C}$; ^1H NMR ($\text{D}_2\text{O}-\text{DCl}$) δ 0.85 (t, 6 H, CH_2CH_3), 1.35-1.85 (m, 4 H, CH_2CH_3), 2.90-3.27 (m, 8 H, CH_2CH_3), 7.20-7.79 (m, 3 H (Ar)); IR (Nujol) 1740, 1710, 3450 cm^{-1} . Anal. ($\text{C}_{17}\text{H}_{21}\text{N}_2\text{O}_6 \cdot 0.25 \text{H}_2\text{O}$) C, H, N.

2-Nitro-6-[2-(di-n-propylamino)ethyl]phenylacetic Acid Hydrochloride (10a). To a cold (10°C) mixture of 28.0 g (0.0773 mol) of 9a in 400 mL of 2% NaOH (0.20 mol) was added 13.7 mL (0.159 mol) of 30% H_2O_2 . After addition was completed the solution was brought to room temperature and stirred for 1 h.

(27) Kende, A. S.; Hodges, J. C. *Synth. Commun.* 1982, 12, 1-10.

(28) Teitel, S.; O'Brien, J. P. *J. Org. Chem.* 1976, 41, 1557-1558.

(29) Asham, V.; Deeks, R. H. L. *J. Chem. Soc. C* 1959, 1935-1936.

The pH was adjusted to 1.5 by careful addition of concentrated HCl. The volume was reduced in vacuo and the solution cooled to room temperature to give 18.5 g of 11a. A second crop, 2.77 g, was obtained when the filtrate was cooled overnight at 10 °C; total yield 21.26 g (80%), mp 188–192 °C. ¹H NMR (D₂O) δ 0.83 (t, 6 H, CH₂CH₃), 1.42–1.92 (m, 4 H, CH₂CH₂), 3.00–3.50 (m, 8 H), 3.99 (s, 2 H, CH₂CO), 7.30–7.89 (m, 3 H (Ar)). Anal. (C₁₅H₂₁N₃O₂·HCl) C, H, N.

4-[2-(Di-*n*-propylamino)ethyl]-2-(3*H*)-indolone Hydrochloride (28). A mixture of 2.0 g (0.0058 mol) of 10a and 0.205 g of 5% Pd/C catalyst in 100 mL of EtOH was hydrogenated at room temperature and 50 psi for 5 h. The catalyst was removed and the solution concentrated in vacuo to a white powder. Crystallization from 400 mL of CH₂Cl₂ gave 22, which was identical in all respects with material prepared via Scheme I.

4-Methoxy-*N*-*n*-propylphenethylamine Hydrochloride (6). Reaction of 50 g (0.32 mol) of 4-methoxybenzylamine and 51.5 g (0.31 mol) of propionyl chloride was carried out as described for 7a to give 56.5 g (82%) of white crystalline *N*-[2-(4-methoxyphenyl)ethyl]propanamide, mp 75–77 °C. Crystallization of a small sample from CH₂Cl₂-hexane gave crystals, mp 78–79.5 °C. Anal. (C₁₂H₁₇NO₂) C, H, N. Reduction of 50.0 g (0.24 mol) of the amide was carried out as described for 8a to give 43.4 g (79%) of white crystalline hydrochloride, mp 203–211 °C after recrystallization from EtOH-Bz₂O. Anal. (C₁₂H₁₇NO₂·HCl) C, H, N.

N-(4-Methoxyphenethyl)-*N*-(2-methyl-3-nitrophenethyl)-*N*-*n*-propylamine (8b). The reaction of 23.5 g (0.10 mol) of 6 with the acid chloride prepared from 20 g (0.102 mol) of 2-methyl-3-nitrophenylacetic acid was carried out essentially as described for the preparation of 7a to give the crude amide as an oil, which was used without further purification. It was reduced with borane in THF as described for 8a to give 27.4 g (79.5%) of 8b as an amber oil after Kugelrohr distillation (bp 200 °C (1.5 mmHg)). Anal. (C₂₂H₂₉N₃O₄) C, H, N.

2-Nitro-6-[2-[*N*-(4-methoxyphenethyl)-*N*-*n*-propylamino]ethyl]phenylacetic Acid Hydrochloride (10b). This Reissert reaction was carried out with 10.0 g (0.028 mol) of 8b by using the procedure described for the preparation of 9a to give 5.3 g (41%) of the crude hydrochloride of the phenylpyruvic acid as a buff powder. It melted at 174 °C dec after crystallization from EtOAc. A total of 5.6 g (56%) of crude unreacted starting material was also obtained. A total of 8.3 g (0.018 mol) of the crude phenylpyruvic acid was converted to the acetic acid as described for 10a. The hydrochloride of the acetic acid was soluble in CHCl₃ and the crude product was isolated as a foam (8.2 g) by concentrating a solution of the hydrochloride in CHCl₃. An analytical sample, mp 114–119 °C dec, was obtained by concentrating to dryness a CH₂Cl₂ solution of the sodium salt and titration with a small volume of dilute HCl. Anal. (C₂₂H₂₅N₃O₆·HCl·0.5H₂O) C, H, N.

4-[2-[*N*-(4-Methoxyphenethyl)-*N*-*n*-propylamino]ethyl]-2-(3*H*)-indolone Hydrochloride (33) and 1-Hydroxy-4-[2-[*N*-(4-methoxyphenethyl)-*N*-*n*-propylamino]ethyl]-2-(3*H*)-indolone Hydrochloride (35). A mixture of 6.2 g (0.014 mol) of crude 10b, 250 mL of EtOH, 2 mL of concentrated HCl, and 700 mg of 5% Pd/C catalyst was hydrogenated at room temperature and 50 psi for 6 h. After removal of the catalyst, the solvent was removed in vacuo. Column chromatography (silica gel 60, 150 g, 70–230 mesh, E. Merck) using CHCl₃-MeOH (95:5) and collecting 40-mL fractions gave 1.04 g of 33 and 1.8 g of 35 as powders.

N-[2-[4-[(Hydroximinooacetyl)amino]phenyl]ethyl]-2,2,2-trifluoroacetamide (12). Amine 11³⁰ (9.77 g, 0.042 mol), dissolved (80 °C) in 150 mL of H₂O containing 50 mL of H₂SO₄, was reacted with chloral hydrate (7.2 g, 0.044 mol) and hydroxylamine sulfate (20.98 g, 0.128 mol) as described in the preparation of 4. Buff crystals of 12 were obtained upon cooling, 7.9 g (62%). An analytical sample, mp 176–176 °C, was obtained by crystallization from EtOAc-hexane. Anal. (C₁₇H₁₇F₃N₃O₅) C, H, N.

5-[2-(Trifluoroacetamido)ethyl]isatin (36). Compound 12 (7.9 g, 0.042 mol) was added rapidly in portions with stirring to

85 mL of concentrated H₂SO₄ at 80 °C. After 6 min the solution was poured over ice and the solid product extracted into EtOAc. The EtOAc solution was concentrated to 100 mL and cooled; 6.1 g of orange/red 36.

5-(2-Aminoethyl)-2-(3*H*)-indolone Hydrochloride (38). Isatin 35 (2.62 g, 9.57 mmol) was catalytically reduced by method A used for the synthesis of 16 to give 37 as a white crystalline solid, mp 203–204 °C. A solution of 37 (0.5 g, 0.001 mol) in a mixture of 10 mL of 10% HCl and 10 mL of EtOH was refluxed for 16 h and concentrated to dryness in vacuo to give 38.

6-(2-Hydroxyethyl)-2-(3*H*)-indolone Methanesulfonate (40). A solution of borane in THF (0.021 mol) was added with stirring to a suspension of 2.0 g (0.011 mol) of indolone-6-acetic acid³¹ in 100 mL of THF. After the mixture was stirred for 16 h, 25 mL of MeOH was added, and the solvents were removed in vacuo. The residue was again stirred with a small volume of MeOH and concentrated in vacuo to give a pale green solid. Chromatography on 106 g of silica gel 60 (70–230 mesh, E. Merck) with a MeOH-CHCl₃ gradient and elution with 20% MeOH-CHCl₃ gave 1.04 g (46%) of 6-(2-hydroxyethyl)-2-(3*H*)-indolone. To a solution of 1.0 g (0.0057 mol) of this carbinal in 5 mL of pyridine was added 0.55 g (0.0057 mol) of methanesulfonyl chloride in one portion with ice cooling. This solution was stirred at room temperature for 2 h and then poured into dilute HCl and extracted with CH₂Cl₂. The CH₂Cl₂ solution was extracted with 10% HCl and brine and then dried (MgSO₄). Removal of the CH₂Cl₂ gave 1.12 g of 40 as a pale orange solid.

6-[2-(Di-*n*-propylamino)ethyl]-2-(3*H*)-indolone Hydrochloride (41). A solution of mesylate 40 (0.88 g, 0.0035 mol) in a mixture of 8.8 mL of MeOH and 8.8 mL of di-*n*-propylamine was stirred in a sealed vessel at 100 °C for 2.5 h. The volatile liquids were removed in vacuo, H₂O was added, and the mixture was made alkaline with 10% NaOH and extracted with ether. Addition of HCl gas to the ether solution gave pink crystals of 41.

4-Methoxy-*N*,*N*-di-*n*-propylphenethylamine (42). To a solution of 30 g (0.3 mL) of di-*n*-propylamine in 70 mL of CHCl₃ was added at 0 °C a solution of 18.4 g (0.1 mol) of 4-methoxyphenylacetyl chloride in 70 mL of CHCl₃. The mixture was heated at 50 °C for 2 h and then concentrated in vacuo. The residue was dissolved in CHCl₃ and extracted with 10% HCl, 5% Na₂CO₃, and H₂O. After drying (MgSO₄), the CHCl₃ was removed in vacuo to give 23.6 g (95%) of crude amide as a viscous oil, which was used without further purification. To a solution of 0.95 M diborane in THF (750 mL, 0.735 mol) was added with stirring a solution of 127.2 g (0.51 mol) of crude amide in 300 mL of THF. The mixture was refluxed for 4 h, and after cooling, 50 mL of MeOH was added and stirring was continued for 60 h. The solvents were removed in vacuo, and the oily yellow residue was heated with dilute (10%) HCl on the steam bath for 2 h. This solution was cooled and extracted with Et₂O and the aqueous phase was made basic with 40% NaOH. The oily product was extracted into Et₂O, and after drying (MgSO₄), the ether was removed in vacuo to give 101 g of yellow oil. Distillation at 0.5 mm gave 90.3% (76%) of clear oil, bp 113–116 °C. Anal. (C₂₂H₂₉NO) H, N, C: calcd, 76.55; found, 75.70.

4-Hydroxy-3-nitro-*N*,*N*-di-*n*-propylphenethylamine (44). To a solution of 20 g (0.095 mol) of 43 in 150 mL of HOAc was added with stirring 8.42 g (5.97 mL, 0.095 mol) of 70–71% HNO₃. The solution was stirred overnight at room temperature, then diluted with water and neutralized with NH₄OH. The oily product was extracted into EtOAc. Purification using dry column chromatography (silica gel, 10% MeOH-EtOAc) gave 11.8 g of a dark amber oil, which crystallized on standing.

3-Amino-4-(benzyloxy)-*N*,*N*-di-*n*-propylphenethylamine Dihydrochloride (45). A mixture of 23.5 g (0.088 mol) of 44, 40 g (0.29 mol) of K₂CO₃, and 10.5 mL (15.1 g, 0.088 mol) of benzyl bromide in 300 mL of acetone was refluxed for 2 h. After filtration, the acetone was removed in vacuo and the residue dissolved in warm EtOAc and cooled. A small amount of quaternary salt was removed by filtration and the filtrate concentrated in vacuo to give 30.2 g of an orange oil. Purification by dry column chro-

(30) Foye, W. O.; Anderson, J. C. *J. Pharm. Sci.* 1959, 58, 1552–1559.

(31) Ruggli, P.; Bossemaker, B. B.; Müller, W. *Helv. Chim. Acta* 1935, 18, 613–622.

matography (silica gel, 50% Et₂O-petroleum ether) gave 23.1 g (73.5%) of 4-(benzylxy)-3-nitro-*N,N*-di-*n*-propylphenethylamine, which was used without further purification. To a solution of the 23.1 g (0.055 mol) of the above nitro compound in 100 mL of MeOH was added 0.35 g of PtO₂ and sufficient dry HCl gas in Et₂O to partially neutralize the amine. The mixture was hydrogenated at 60 psi with shaking. The catalyst was removed by filtration and the solvent by evaporation in vacuo. The residue was dissolved in *i*-PrOH and made acidic by the addition of ethereal HCl. Et₂O was added slowly, and the salt was filtered; 24.3 g (93%, 71% overall).

3-Formamido-4-hydroxy-*N,N*-di-*n*-propylphenethylamine Hydrochloride (45). A solution of 5.0 g (0.015 mol) of the free base of 45 in 150 mL of ethyl formate was refluxed overnight. The ethyl formate was removed in vacuo and the residual oil dissolved in EtOAc/Et₂O. A small amount of white solid was removed by filtration, and the solvents were again removed in vacuo. This crude product (5.2 g) was used without further purification. A solution of 1.75 g (0.0049 mol) of the above crude formyl derivative in 50 mL of MeOH containing a small amount of EtOAc was hydrogenated at 60 psi with shaking in the presence of 0.75 g of 10% Pd/C. After 1 h the catalyst was removed by filtration and the solvents were removed by evaporation in vacuo to give 1.3 g of an oily product. It was converted to the hydrochloride salt by the addition of ethereal HCl to a solution in MeOH, 0.925 g.

3-Acetamido-4-hydroxy-*N,N*-di-*n*-propylphenethylamine Hydrochloride (47). A solution of 2.1 g (0.0054 mol) of the free base of 45 in 75 mL of Ac₂O was stirred overnight at room temperature. The Ac₂O was removed in vacuo to give 2.4 g of a tan oil. This oil was dissolved in a mixture of 50 mL of MeOH and 10 mL of EtOAc and hydrogenated with shaking at 60 psi in the presence of 1.0 g of 10% Pd/C. The catalyst was filtered and the filtrate was concentrated to an oil in vacuo. This was converted to the hydrochloride in methanol with use of ethereal HCl, 1.75 g.

Assay for Inhibition of Adrenergic Neurotransmission in the Isolated Perfused Rabbit Ear Artery (EIRA). A 2-4-cm segment of central ear artery is mounted in a narrow cylindrical chamber where it is simultaneously perfused intraluminally and superfused extraluminally with oxygenated Krebs solution. Drugs can be administered by means of either the intraluminal or extraluminal flow. Changes in arterial diameter are reflected as changes in intraluminal perfusion pressure. At 4-min intervals, the vascular sympathetic nerves are excited by pulses from an electronic stimulator delivered through platinum electrodes

present in the chamber. The test drug is administered in increasing concentration. Each concentration is allowed to remain in contact with the tissue for 4 min. The drug concentration is increased immediately following the response to nerve stimulation. If the effect of dopaminergic blockade is to be determined (S)-sulpiride superfusion is begun after obtaining the initial concentration-effect curve for the test compound. Following a 30-min equilibration period, the curve is repeated in the presence of (S)-sulpiride.

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Registry No. 1, 81654-47-9; 2, 81654-48-0; 3, 81654-49-1; 4, 85763-09-3; 5, 101566-00-1; 6-HCl, 101566-01-2; 7a, 91374-22-0; 8a, 91374-23-1; 8b, 101566-02-3; 9a, 97351-95-6; 10a, 91374-25-3; 10b, 101566-03-4; 11, 24954-62-9; 12, 101566-04-5; 13, 101566-05-6; 14, 81654-50-4; 14, 81654-50-4; 15, 101566-06-7; 16, 101566-07-8; 17-HCl, 101566-08-9; 18, 101566-09-0; 18-HBr, 101566-10-3; 19, 81654-51-5; 20, 81654-52-6; 21, 81654-54-8; 21-HCl, 81654-53-7; 22, 85763-08-2; 22-HBr, 81654-59-3; 23-HCl, 101566-11-4; 24, 101566-12-5; 24-HBr, 101566-13-6; 25, 85763-10-6; 25-HCl, 81654-56-0; 26, 81654-62-8; 26-HBr, 81654-57-1; 27-HCl, 91374-19-5; 28, 91374-21-9; 28-HCl, 91374-20-8; 29-HCl, 101566-14-7; 30, 101566-15-8; 31, 101566-16-9; 31-HBr, 101566-17-4; 32, 101566-18-1; 33, 101566-19-2; 33-HCl, 101566-20-5; 34, 101566-21-6; 34-HBr, 101566-22-7; 35-HCl, 101566-23-8; 36, 101566-24-9; 37, 101566-25-0; 38, 101566-26-1; 38-HCl, 101566-27-2; 39, 101566-28-3; 39-HCl, 101566-29-4; 40, 101566-30-7; 41, 101566-31-8; 41-HCl, 101566-32-9; 42, 95838-46-2; 43-HBr, 101566-33-0; 44, 95838-47-4; 45-2HCl, 95838-48-5; 46, 101566-34-1; 46-HCl, 101566-35-2; 47, 101566-36-3; 47-HCl, 101566-37-4; 4-methoxybenzenesethanamine, 55-51-2; propionaldehyde, 123-38-6; 1,2-ethanedithiol, 540-63-6; 4-methylphenylacetaldehyde, 5703-26-4; 5-chloro-1-phenyl-1H-tetrazole, 14210-25-4; 2-methyl-3-nitrophenylacetic acid, 23876-16-5; 4-methoxybenzenesethanamine, 55-51-2; propionyl chloride, 79-03-8; *N*-(2-(4-methoxyphenyl)ethyl)propionamide, 67191-51-9; phenylpyruvic acid, 156-06-9; 6-(2-hydroxyethyl)-2(3H)-indolone, 101566-38-5; 4-methoxyphenylacetyl chloride, 4593-91-8; 4-(benzylxy)-3-nitro-*N,N*-di-*n*-propylphenethylamine, 95838-51-0.

Synthesis, Saluretic, and Antihypertensive Activity of 6,7-Disubstituted 1(2*H*)- and 3,4-Dihydro-1(2*H*)-phthalazinones

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The synthesis of the isomeric series 6-chloro-7-sulfamoyl- and 7-chloro-6-sulfamoyl-1(2*H*)-phthalazinones (1 and 2) and 6-chloro-7-sulfamoyl- and 7-chloro-6-sulfamoyl-3,4-dihydro-1(2*H*)-phthalazinones (3 and 4), combining structural features characteristic to furosemide and hydralazine, is described, the mechanism of the formation of 1 and 2 is discussed, and their structure-activities relationships are studied. Preliminary screening in the rat shows that series 1 and 3 exhibit diuretic and saluretic activity similar to that of chlorothiazide with, however, Na⁺/K⁺ ratios more favorable than chlorothiazide and furosemide. The compounds of series 2 and 4 are practically inactive. All four series show initial antihypertensive activity lower than that of hydralazine. However, compounds 1e, 1c, and 4a show a higher activity at 8 and/or 24 h after administration and thus may offer a unique combination of a "loop" diuretic with direct long-acting peripheral vasodilating effects.

Many diuretics and saluretics possess an aromatic nucleus with a halogen, pseudohalogen, or a phenoxy group in the position ortho to and an electronegative group in the position meta to a sulfonamide group.¹ Among those that have found wide use are furosemide (5), chlorothiazide

(6), hydrochlorothiazide (7), and bumetanide (15) (Figure 1).

Compounds having cyclic or exocyclic -N-N- moieties (hydralazine, dihydralazine, compounds 11-14²⁻⁴) are

(1) Feit, P. J. Med. Chem. 1971, 14, 432.

(2) Kikuo, A.; Kiyochi, S. Jpn. Patent 7455680; Chem. Abstr. 1974, 81, 135157.

REDACTED

EXHIBIT J

REDACTED

REDACTED

EXHIBIT K

REDACTED